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Research Article

Preoperative paracetamol infusion reduces sevoflurane consumption during thyroidectomy under general anesthesia with spectral entropy monitoring

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KEYWORDS

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Abstract *Background:* Intravenous (IV) paracetamol has a significant opioid-sparing effect. We investigated the effect of paracetamol infusion on sevoflurane consumption during entropy monitored general anesthesia.

Methods: Sixty-two ASA I and II patients undergoing thyroidectomy under general anesthesia were included in a prospective, randomized, double-blind and placebo controlled study. The patients were randomized to receive a slow infusion of either 1 g paracetamol (paracetamol group, $n = 31$) or saline (control group, $n = 31$) just before induction of anesthesia. Sevoflurane concentration was titrated to keep the state entropy value between 40 and 50. End-tidal sevoflurane concentration, sevoflurane consumption, recovery characteristics, time to first analgesic request and meperidine consumption during the first 6 postoperative hours were recorded.

Results: The mean ± SD estimated sevoflurane consumption was significantly lower in the paracetamol treated patients (36.2 ± 15 vs 44.9 ± 13.9 ml, in the control group; $p = 0.021$). Patients receiving paracetamol had a faster post-anesthetic recovery profile (extubation time, time to eye opening to command and time to state name and mention his/her home address) than the other

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group ($p < 0.05$). Mean ± SD time to first analgesic request was significantly prolonged in paracetamol group compared to control group (48.4 ± 14.0 vs 40.7 ± 11.5 min, respectively; $p = 0.021$). Meperidine consumption was higher in control group than in paracetamol group (28.7 ± 10.2 vs 23.1 ± 9.0 mg, respectively; $p = 0.025$).

Conclusion: Preoperative IV paracetamol infusion improved consumption and emergence from entropy monitored sevoflurane anesthesia with enhancement of the early postoperative analgesia.

1. Introduction

Proper monitoring of the depth of anesthesia is crucial for judicious titration of anesthetics to prevent awareness under general anesthesia as well as the side effects of anesthetic over-dose with the subsequent economic waste and environmental pollution. With awareness, the patient may exhibit symptoms ranging from mild anxiety to post traumatic stress disorder (sleep disturbances, nightmares and social difficulties) [1]. In the standard clinical practice, the depth of anesthesia is judged by the clinical experience of the anesthetist, based on the patient's vital signs and the hemodynamic responses. However, the regular use of certain medications as β-blockers and antihypertensive drugs render the hemodynamic signs unreliable for titration of anesthetics [2].

At present; the electroencephalogram (EEG) based spectral entropy is increasingly being used for monitoring the depth of anesthesia and provides information regarding the cortical state of the patient and the level of hypnosis [3] as well as an indirect measure of the adequacy of analgesia [4]. The monitor uses different algorithms to calculate the level of consciousness index by processing the EEG signal measured over the forehead and drive the numeric index [5]. The spectral entropy has 2 signals: State entropy (SE) which reflects the hypnotic level of the patient; computed from an EEG data from the previous 15 s in the range of 0.8–32 Hz, and shows the value in the range of 0–91 and Response entropy (RE) that includes; in addition to the EEG, a forehead muscle electromyography component and reflects the patient arousal and response to painful stimuli. The latter is computed from an EEG data in the range of 0.8–47 Hz and shows the value in the range of 0–100 [6]. State entropy values between "40–60" are the recommended surgical level of anesthesia while "100" signifies awake state and "0" indicates suppression of the cortical neuronal activity [7].

Intravenous (IV) paracetamol (acetaminophen in USA) is an effective analgesic and antipyretic agent acting at both the central and peripheral components of the pain pathway [8] and devoid of the detrimental effects of opioids and non-steroidal anti-inflammatory drugs (NSAID) with a tolerability profile similar to placebo [9]. The onset of paracetamol analgesia starts rapidly after 5–10 min of IV administration, with peak effect obtained within 1 h and lasting 4–6 h. [10] Thus, IV paracetamol is a suitable medication for the treatment of postoperative pain when used either alone or as a part of a balanced analgesic regimen. Moreover, several studies in the medical literature have demonstrated the opioid-sparing effect of IV paracetamol [11–15]. In view of these reports; we hypothesized that preoperative infusion of IV paracetamol would decrease sevoflurane consumption during general anesthesia. To explore this; we designed a prospective, randomized, double-blind and placebo controlled study to evaluate the effect of the preoperative single-dose administration of IV paracetamol on sevoflurane consumption in patients undergoing thyroidectomy under general anesthesia with an entropy added to the standard intraoperative monitors.

2. Methods

This study took place in king Abdulaziz Naval Base Hospital, Jubail, Kingdom of Saudi Arabia, from May 2011 to April 2013. The protocol was approved by the Hospital Ethics Committee and written informed consent was obtained from each patient. The study was registered at the Australian New Zealand Clinical Trial Registry (ANZCTR). URL and unique identification number: http://www.ANZCTR.org.au/ACTRN12613000485730.aspx. We studied 62 ASA physical status I and II patients of both sex, aged 20–55 years scheduled for subtotal thyroidectomy under general anesthesia. All enrolled patients were euthyroid. Patients were excluded if they had known allergy to paracetamol, neurological or psychological diseases, impaired liver functions (Alanine Transaminase > twice the normal value) and impaired renal function (serum creatinine > 2.0 mg%). Exclusion criteria also included pregnancy and breast feeding, the chronic use of analgesics or drugs affecting the central nervous system (CNS) function, the use of paracetamol within 6 h or any other analgesic medication within 12 h before the operation.

The patients were premedicated with lorazepam 2 mg orally on the evening of operation, and had been fasting for 8 h before surgery. At the operating theatre, all patients had a venous cannula inserted into one of the veins of the dorsum of the hand and IV fluid (lactated Ringer' solution) started at a rate of 7 ml kg h^{-1}. Intraoperative vitals monitoring [electrocardiogram (ECG), noninvasive systolic and diastolic blood pressure (Systolic and Diastolic BP), peripheral oxygen saturation (SpO_2) were applied. After wiping the skin with alcohol, the entropy sensor (Entropy sensor, Disposable. Datex-Ohmeda, Instrumentarium Corp. Helsenki, Finland) was applied to the patient's forehead (approximately 4 cm above the nose) and the temple area (between the corner of the eye and the hairline). The sensor was connected to the Datex-Ohmeda M-Entropy module via the Datex-Ohmeda ENT-3 Entropy sensor cable.

Before the start of anesthesia, the patients were randomized, by using a computer generated random list to one of two groups; the Paracetamol group (Group P) and the Control group (Group C). All patients received a slow IV infusion over 15 min just before induction of anesthesia of either 1 g paracetamol (Perfalgan 10 mg ml^{-1}, 100 ml vial; UPSA, France) (Group P, $n = 31$) or 100 ml of normal saline (Group C, $n = 31$). Blinding was carried out by a technician, not involved

in the data collection, who made up identical infusions of paracetamol and 0.9% normal saline in equal volumes under sterile conditions. Anesthesia was induced with fentanyl 1.5 μg kg^{-1} and propofol 1 mg kg^{-1}. Tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. Oxygen and nitrous oxide mixture (40:60% respectively) with sevoflurane 1.5 volume% in 3 L min^{-1} fresh gas flow were used for maintenance of anesthesia. Sevoflurane concentration was titrated by 0.5 volume% every 5 min to allow the SE value to range between 40–50. However, when the hemodynamic parameters could not be maintained (hypotension or bradycardia which were defined as a 30% reduction of the baseline values); vasoactive drugs were used as indicated according to the usual clinical practice. The patients were also monitored for signs of inadequate anesthesia during surgery (tachycardia and hypertension [30% increases from baseline values], pupillary dilatation, lacrimation, sweating, grimacing, movement, eye opening or coughing) which were managed by increasing sevoflurane concentration. Intermittent doses of atracurium to maintain muscle relaxation were given to a single twitch of the train of four and mechanical ventilation started with respiratory rate 12 min^{-1} and tidal volume 5–7 ml kg^{-1} to keep the end tidal carbon dioxide ($ETCo_2$) at 30–35 mmHg. Intraoperative vital data (ECG, heart rate [HR], Systolic and Diastolic PB, SpO_2 and the end-tidal sevoflurane concentration [$sevoflurane_{ET}$]) were recorded by an anesthesia technician not aware of the treatment groups; immediately after endotracheal intubation, at 5 min intervals throughout the first operative hour, at the start of skin closure and on completion of surgery.

After application of the surgical dressing, sevoflurane administration was stopped, and atropine 10 μg kg^{-1} and neostigmine 50 μg kg^{-1} were used to antagonize the residual neuromuscular block. The trachea was extubated after recovery of adequate spontaneous ventilation. Extubation time, time to eye opening to command, time to state his/her name and time to correctly mention his/her home address (assessed at 60 s intervals) were noted and taken from cessation of sevoflurane inhalation. Sevoflurane consumption was estimated for each patient by the "vaporizer weighing method" in which the vaporizer was filled to maximum and weighed using a sensitive balance (Triple Beam Balance 700/800 Series, OHaus Corporation, Florham Park, N.J. 07932, USA) before induction of anesthesia, then reweighed again at the completion of surgery. By knowing the specific weight of sevoflurane (1.52 kg L^{-1}) [16]; the volume of the consumed liquid sevoflurane was estimated.

Following surgery, the patients were transferred to the post anesthesia care unit (PACU) where they were monitored and received oxygen via a face mask at 6 L min^{-1}. Pain intensity was assessed immediately by the nurses who were blinded to the treatment group using a 10-cm visual analogue scale (VAS) on which 0-cm indicated no pain and 10-cm the worst imaginable pain and was re-assessed again in the surgical ward, every 2 h till the end of the 6th postoperative hour. Meperidine IV bolus 20 mg was administered when the VAS >3 or when requested by the patient and could be repeated every 10 min until VAS is 3 or less, with a maximum dose not more than 1 mg/kg. Time to the first analgesic demand (defined as the period between tracheal extubation to the first administration of analgesic medication) was recorded. Total doses of meperidine given in the PACU and surgical ward were calculated. If pain scores remained >3 more than 30 min; IV lornoxicam 8 mg was used as a rescue analgesic and could be repeated once more after a lockout time of 1 h.

The degree of sedation was recorded on admission to the PACU and at the 2nd, 4th and 6th postoperative hour using a four-points scale: 0 = awake and alert, 1 = drowsy, 2 = mostly sleeping, 3 = difficult or impossible to awaken.

The frequency and severity of postoperative nausea and vomiting (PONV) were observed and documented; with no differentiation had been made between retching and vomiting till the end of the 6th postoperative hour as follows: 0 = no nausea, 1 = mild-moderate nausea, 2 = mild vomiting (once per observational period) with severe nausea, 3 = moderate vomiting (twice per observation period), 4 = severe vomiting (3–4 times per observation period). For moderate and severe vomiting, ondansetron 4 mg IV injection was used as a rescue antiemetic.

Other side effects including bradycardia, hypotension, respiratory depression (persistent respiratory rate <10 breaths min^{-1} or oxygen saturation $<90\%$ without oxygen supplementation), headache, malaise, anxiety, muscle spasm and adverse reactions at the injection site (pain, burning sensation, erythema and pruritus) were recorded for each patient, and suitable treatment was given if indicated. The next day of surgery, the patients were questioned about having nightmares or dreams and whether they could recall any intraoperative event.

3. Statistical methods

The required sample size was calculated using G*Power software version 3.1.3 (Heinrich Heine Universität, Institut für Experimentelle Psychologie, Düsseldorf, Germany). The primary outcome measure was the difference in end-tidal sevoflurane between the two study groups. It was estimated that a sample of 30 patients in each study group would achieve a power of 81% to detect a medium effect size (d) of 0.35 as regards the primary outcome measure using a two-sided unpaired t test and setting the type I error at 0.05.

Statistical analysis was done on a personal computer using GraphPad© Prism© version 6.01 (GraphPad© Software Inc., La Jolla, California, USA). Numerical data are presented as mean (SD) and intergroup differences are compared with the independent-samples t test. Categorical data are presented as ratio or as number (%) and between-group differences are compared using the Pearson chi square test or the chi square test for trends for nominal or ordinal data, respectively. Fisher's exact test is used in place of the chi square test if $>20\%$ of cells in any contingency table had an expected count of <5.

A two-side $P < 0.05$ is considered statistically significant.

4. Results

All patients completed the study. The patients' characteristics were comparable in the 2 groups. There were no statistical differences between both groups in the mean baseline values of the hemodynamic and respiratory parameters. The duration of surgery and anesthesia was similar in the studied groups (Table 1).

Intraoperative hemodynamic monitoring revealed no significant differences in the 2 groups ($p > 0.05$) and no patient received vasoactive drugs for hemodynamic instability. There were statistically significant differences in the post-anesthetic

Table 1 Patient characteristics and operative data.

Variable	Group P (n = 31)	Group C (n = 31)	P value
Age (year)	32.2 (3.4)	31.9 (3.1)	0.718
Gender (male/female)	3/28	2/29	1.0
Weight (kg)	65.2 (4.7)	64.9 (4.1)	0.790
Height (cm)	160.9 (5.5)	162.7 (5.6)	0.207
ASA-PS (I/II)	29/2	27/4	0.671
Duration of surgery (min)	103.1 (14.1)	105.7 (12.9)	0.452
Duration of anesthesia (min)	122.6 (4.9)	120.0 (5.4)	0.052
Baseline heart rate (beats/min)	63 (8.0)	65 (9.0)	0.359
Baseline systolic BP (mmHg)	114 (11.0)	117 (14.0)	0.352
Baseline diastolic BP (mmHg)	66.7 (6.0)	68 (4.0)	0.320

Data are presented as mean (SD) or ratio.
Statistical significance at $p < 0.05$.

Table 2 Estimated sevoflurane consumption and post-anesthetic recovery profile.

Variable	Group P (n = 31)	Group C (n = 31)	P value
Estimated sevoflurane consumption (ml)	36.2 (15.0)	44.9 (13.9)	0.021
Extubation time (min)	6.1 (2.9)	7.9 (3.5)	0.031
Time to eye opening (min)	8.2 (2.8)	9.8 (3.2)	0.040
Time to state name (min)	10.4 (2.3)	12.6 (4.5)	0.018
Time to mention home address (min)	12.2 (4.1)	14.8 (4.9)	0.027

Data are resented as mean (SD).
Statistical significance at $p < 0.05$.

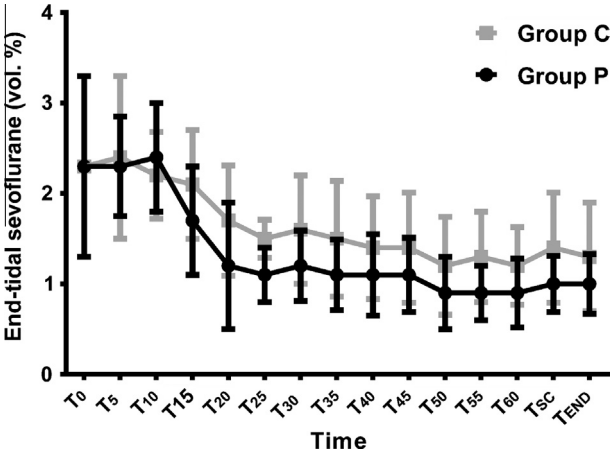

Figure 1 Mean end-tidal sevoflurane concentration in both study groups. Error bars represent SD. ET_{0-60}: End-tidal sevoflurane concentration at 0–60 min after endotracheal intubation. ET_{SC}: End-tidal sevoflurane concentration at skin closure. ET_{END}: End-tidal sevoflurane concentration at the end of surgery.

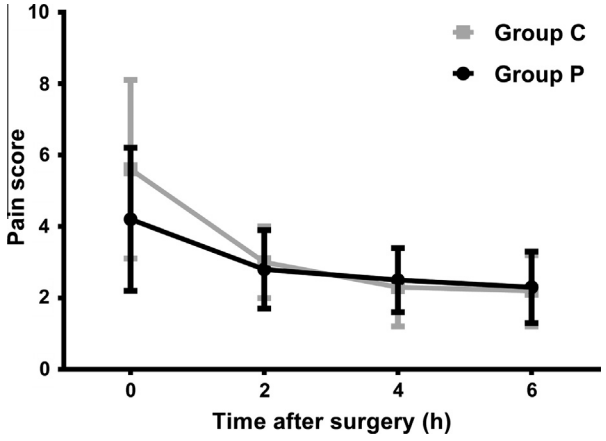

Figure 2 Mean postoperative pain scores in the two study groups. Error bars represent SD.

recovery profile (extubation time, time to eye opening to command, time to state name and time to correctly mention his/her home address) between the paracetamol group and the control group (Table 2). There was a statistically significant difference in end-tidal values of sevoflurane concentration in group P compared to group C ($p < 0.05$). $Sevoflurane_{ET}$ values were higher in the control group during the time periods from 15 min after endotracheal intubation till the end of surgery (Fig. 1). The mean ± SD estimated sevoflurane consumption during surgery was significantly lower in the paracetamol group than in the control group (36.2 ± 15 vs 44.9 ± 13.9 ml, respectively; $p = 0.021$) (Table 2).

The VAS scores of the patients in the control group were significantly higher than those in the paracetamol group on admission to the PACU ($p = 0.018$) and were similar in the 2 groups thereafter (Fig. 2). The mean ± SD time to first analgesic request was significantly prolonged in the paracetamol group compared to the control group (48.4 ± 14.0 vs 40.7 ± 11.5 min, respectively; $p = 0.021$). Analysis of meperidine consumption in the PACU and the surgical ward during the first 6 postoperative hours revealed a statistically significant difference between the 2 groups. The mean ± SD meperidine consumption was higher in the control group than in the

Table 3 Postoperative analgesia.

Variable	Group P (n = 31)	Group C (n = 31)	P value
Time to first analgesic request (min)	48.4 (14.0)	40.7 (11.5)	0.021
Total meperidine consumption (mg)	23.1 (9.0)	28.7 (10.2)	0.025
Need for rescue analgesic (%)	13 (41.9)	18 (58.1)	0.310
Total lornoxicam consumption (mg)	4.9 (1.2)	5.7 (1.4)	0.019

Data are presented as mean (SD) or number (%).
Statistical significance at $p < 0.05$.

Table 4 Incidence of PONV during the first 6 postoperative hours.

PONV score	Group P (n = 31)	Group C(n = 31)	P value
No nausea	15 (48.4)	11 (35.5)	0.337
Mild-to-moderate nausea	8 (25.8)	9 (29)	
Severe nausea, mild vomiting	4 (12.9)	6 (19.4)	
Moderate vomiting	3 (9.7)	3 (9.7)	
Severe vomiting	1 (3.2)	2 (6.5)	

Data are presented as number (%).
Statistical significance at $p < 0.05$.

Table 5 Postoperative sedation scores.

Time	Sedation score	Group P (n = 31)	Group C (n = 31)	P value
Admission to PACU	0	23 (74.2%)	24 (77.4%)	0.845
	1	5 (16.1%)	4 (12.9%)	
	2	3 (9.7%)	3 (9.7%)	
2 h after surgery	0	26 (83.9%)	17 (54.8%)	0.046
	1	3 (9.7%)	11 (35.5%)	
	2	2 (6.5%)	3 (9.7%)	
4 h after surgery	0	28 (90.3%)	23 (74.2%)	0.147
	1	2 (6.5%)	6 (19.4%)	
	2	1 (3.2%)	2 (6.5%)	
6 h after surgery	0	30 (96.8%)	27 (87.1%)	0.165
	1	1 (3.2%)	4 (12.9%)	

Data are presented as number (%).
Statistical significance at $p < 0.05$.

paracetamol group (28.7 ± 10.2 vs 23.1 ± 9.0 mg, respectively; $p = 0.025$). In addition, 18 patients (58%) in the control group received rescue analgesia compared to 13 patients (42%) in the paracetamol group ($p = 0.31$), with a statistically significant difference between both groups in the mean ± SD cumulative doses of lornoxicam used (4.9 ± 1.2 mg in group P vs 5.7 ± 1.4 mg in group C, $p = 0.019$) (Table 3).

There were no statistically significant differences in the postoperative mean HR and mean Systolic and Diastolic BP ($p > 0.05$) between the studied groups. During the first 6 postoperative hours; 2 (6.4%) patients in group P and 3 other patients in group C (9.6%), developed oxygen desaturation in the surgical ward with respiratory depression. They improved by oxygen mask; Venturi 40%, 10 L min^{-1}, with a non-significant difference between the 2 groups ($p > 0.05$). Numerically, more patients in the control group experienced PONV than those receiving paracetamol, but this did not reach statistical significance ($p = 0.337$) (Table 4). There was no significant difference between the groups regarding the mean sedation scores on admission to the PACU ($p > 0.05$), but at the 2nd postoperative hour; the mean scores of sedation were significantly lower in the paracetamol group with no significant differences between the studied groups thereafter till the end of the 6th postoperative hour (Table 5). No patient in either group complained of headache, muscle spasm or local adverse reactions at site of the venous cannula and none of them noted recall of intraoperative events or complained of having nightmares. Ten patients in the paracetamol group (32.2%) and 8 in the control group (25.8%) reported dreaming during sleep, with no statistical significance ($p = 0.780$).

5. Discussion

The results of this study showed that IV administration of 1 g paracetamol before induction of general anesthesia was associated with a significant decrease in sevoflurane consumption during surgery when spectral entropy was added to the standard intraoperative monitoring. This intraoperative reduction in the volatile gas consumption had an impact on the emergence from anesthesia and resulted in acceleration of the post-anesthetic recovery times of the patients.

A swift emergence from general anesthesia and sustained alertness after completion of surgery is of particular importance for earlier maintenance of patent airway, better peripheral oxygen saturation and more protection against pulmonary aspiration. One approach to hasten post-anesthetic recovery is the introduction of the short half-life volatile anesthetics as sevoflurane and desflurane [16]. Sevoflurane has the desirable advantage of a rapid elimination; due to its low solubility in blood that results in a rapid fall in the alveolar anesthetic concentration upon discontinuation and a fast recovery from anesthesia [17]. However, following cessation of sevoflurane administration, complete awakening may require up to 90 min to occur, depending on the amount of residual sevoflurane [16] and during that time; the protective airway reflexes may not be restored. After sevoflurane discontinuation, its level decreases rapidly with a residual 10% persistence after 1 h, and 0.5% tail which may last for the next 8 h. [18] Residual sevoflurane; together with its degradation products, may lead to impairment of the CNS chemosensetivity to hypoxia during recovery [19] and prolongation of the neuromuscular block by relaxants [20]. These effects could be of concern during the post-anesthetic recovery of patients who are vulnerable to postoperative respiratory complications.

The utilization of the EEG based monitors as the bispectral index (BIS) and the spectral entropy for judging the depth of general anesthesia and the level of hypnosis during surgery has been shown to result in reduction of sevoflurane consumption and shorten the recovery time. Pavlin and co-workers [21] reported that the end-tidal sevoflurane concentration was reduced by 13% when BIS monitor was used to titrate the dose of the volatile anesthetic. Aime and colleagues [22] demonstrated that sevoflurane anesthesia using either BIS or an entropy monitor to titrate the administered dose of anesthetics, both monitoring methods equally reduced the administered dose of sevoflurane by 29%. Although the recommended surgical level of general anesthesia for entropy monitor lies between 40–60; we preferred in this study to be more conservative and chose a lower target range of SE between 40–50; to ensure adequate level of hypnosis and to minimize the risk of intraoperative awareness; as its occurrence is often the direct consequence of using insufficient doses of anesthetics or light-anesthetic techniques; taking into consideration some reports of failure of entropy monitor [23,24]. Also, we believe that the use of the processed EEG based monitors to guide the depth of anesthesia could be associated with intentional over-reduction in the anesthetic depth on the basis of the displayed values of these monitors. It is noteworthy that none of our patients noted recall of any intraoperative event, and only a few, in either group, reported the usual dreaming while sleeping during the first postoperative night.

As far as our knowledge, this is the first study in the medical literature that tests the influence of preoperative IV paracetamol infusion on sevoflurane consumption during surgery with spectral entropy monitoring. In this study, sevoflurane consumption was reduced by 19.4% and this was associated with rapid recovery from general anesthesia in the paracetamol treated patients. Intravenous paracetamol is a non-opioid analgesic and antipyretic, recommended world-wide as a first line treatment of pain and fever in adults and children [9] although the precise mechanism of action is still unclear, the agent induces analgesia via inhibition of the central and peripheral cyclo-oxygenase I and II pathways that result in reduced synthesis of prostaglandin E2; one of the primary mediator of nociception [25]. Another hypothesis assumes that paracetamol analgesia is due to its direct inhibition of the N-methyl-D-aspartate (NMDA) receptor, which stimulates substance P-dependent synthesis of nitric oxide, another primary mediator of pain [26]. The central antinociceptive effect of paracetamol may involve the serotonergic system as well through activation of the descending serotonergic pathways which are part of the descending pain system in the dorsal horn of the spinal cord [27]. This assumption was supported by the study of Pickering et al. [28] who revealed that the antagonists of 5-hydroxytryptamine (5-HT_3) receptor; namely tropisetron and granisetron, completely blocked the analgesic effect of paracetamol administered to male adult volunteers. One of the mechanisms involved in the analgesic efficacy of paracetamol is its modulatory effect on endogenous cannabinoid system [29]. The use of IV paracetamol for postoperative pain control is gradually increasing and several studies in the literature have demonstrated the analgesic and the opioid-sparing effect of this agent. Khan and his co-workers [29] in a study of 84 patients undergoing arthroscopic knee surgery showed that patients receiving IV paracetamol had similar pain relief immediately upon arrival in the recovery room and for the next 4 h, compared with those treated with IV morphine. They came to the conclusion that IV paracetamol 1 g was not significantly different from that of morphine 0.1 mg kg^{-1}. Sinatra et al. [11] recorded a significant reduction in morphine consumption over 6 h following the infusion of a single dose of paracetamol 1gm for pain management after major orthopedic surgery. Tsang and colleagues [30] noted a satisfactory pain relief together with a remarkable opioid-sparing effect in 47 preoperative patients with traumatic hip fracture, who were given regular doses of IV paracetamol. In a recent study involving 75 patients who underwent lower limb surgery under spinal anesthesia, Khalili and his colleagues [31] compared the use of a single IV infusion of paracetamol 15 mg kg^{-1} as a preemptive analgesic (given half an hour preoperatively) or as a preventive analgesia (given prior to skin closure). They observed that both preemptive and preventive paracetamol administrations were effective, enhanced the postoperative analgesia and reduced the need for rescue analgesics. Moreover, they found that the total meperidine consumption at 24 h after surgery was lowest in the patients received preemptive paracetamol. In agreement with these trials, the patients receiving IV paracetamol in the current study had improved postoperative analgesia; in addition to their fast emergence from general anesthesia. They had significantly lower VAS scores on admission to the PACU compared to the control group and required a lower cumulative amount of meperidine and lornoxicam, which strongly supports the opioid-sparing effect of IV paracetamol. Furthermore, the patients treated with paracetamol had better postoperative scores of sedation and PONV compared to the control group, which could be attributed to their lower consumption of IV meperidine throughout the early postoperative period.

The onset of paracetamol analgesia after IV administration occurs rapidly within 5–10 min [10]. Paracetamol does not extensively bind to plasma protein and exhibits rapid penetration into the cerebrospinal fluid, with peak analgesic effect obtained within 1 h and the duration of its effect lasting for approximately 4–6 h [8]. It has to be noted that the improvement in pain scores and analgesic consumption in the current

study over the first 6 postoperative hours was longer than expected and could not be attributed to the systemic effects of just a single IV dose of paracetamol. Nevertheless, this prolonged paracetamol analgesia could be explained in terms of preemptive analgesia; which enrolls the use of analgesics and/or anesthetics before elicitation of painful stimuli to prevent or reduce subsequent pain. Thus, if detection of painful stimuli is prevented during surgery, the postoperative pain should be minimized. We therefore, share the view of other authors [31,32] that the preemptive treatment of postoperative pain may substantially reduce the analgesic requirement after surgery. Another possible explanation would be the potent analgesic effect of the metabolite of paracetamol. The agent is thought to influence the endogenous cannabinoid system via an active metabolite (P-aminophenol) which is conjugated with arachidonic acid by fatty acid amide hydrolase to form AM404, (also known as N-arachidophenolamine) [33]. AM404 prevents the reuptake of the endogenous cannabinoids like anandamide from the synaptic cleft [34]. This neurotransmitter is an eicosanoid, synthesized on demand and expresses agonistic activity at the cannabinoid receptors. At least 2 cannabinoids receptor types exist in the mammalian tissues, CB1 and CB2, and activation of these receptors appears to ameliorate pain and inflammation [35].

It has been suggested that supplementation of sevoflurane anesthesia by continuous intraoperative infusion of remifentanil resulted in reduction of the volatile gas consumption and speeding up emergence from general anesthesia. Sert and his colleagues [36] concluded that the use of low flow sevoflurane anesthesia combined with continuous intraoperative remifentanil infusion during tympanoplasty resulted in a faster early recovery and decreased sevoflurane consumption. Similarly, Kim et al. [7] in a study of 40 females undergoing gynecological surgery with entropy monitored general anesthesia, demonstrated that the end-tidal sevoflurane concentration as well as the total volatile gas consumption had been reduced by continuous intraoperative remifentanil infusion. We agree with those authors [7,36] in the context that reducing the consumption of the inhalational anesthetics without compromising both the clinical outcome and the patient satisfaction is highly desirable in order to facilitate earlier recovery from general anesthesia and to minimize the environmental pollution and the economic waste. In the present study, we used the spectral entropy monitoring to titrate the sevoflurane concentration to the desirable depth of anesthesia. Although remifentanil was found to effectively decrease sevoflurane consumption; we used the non-opioid analgesic paracetamol in our trial to reduce the volatile gas consumption during surgery. Remifentanil is a selective μu-opioid receptor agonist that provides intense analgesia of rapid onset and ultra-short duration and is commonly used as a supplemental drug for general anesthesia. [37] Nevertheless, being a μu-receptor agonist, the agent has side effects as bradycardia, hypotension, respiratory depression and PONV and due to its pharmacokinetic characteristics, emergence from remifentanil-based anesthesia is very rapid and can result in severe pain during the early postoperative period [38]. On the other hand certain pharmacodynamics and pharmacokinetics rendered IV paracetamol a favorable choice for us to test its efficacy in reducing volatile gas consumption rather than remifentanil, namely its ease of administration compared to that of remifentanil (as the continuous intraoperative infusion of a medication is cumbersome), the rare occurrence of side effects with a tolerability profile similar to placebo, and its ability to provide effective postoperative analgesia. This last effect of paracetamol is of utmost importance as postoperative pain is the most common undesirable outcome for patients undergoing surgical procedures and can delay recovery from general anesthesia and prolong hospital stay [39].

In conclusion, we demonstrated that the preoperative IV paracetamol infusion improved consumption and emergence from entropy-monitored sevoflurane anesthesia in patients undergoing subtotal thyroidectomy, together with enhancement of the early postoperative analgesia and reduction of rescue analgesics requirement. Further studies are needed to confirm these results in different surgeries.

Conflict of interest

No conflict of interest.

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